(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 464 307 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
06.10.2004 Bulletin 2004/41

(51) Int Cl.[7]: **A61F 2/44**, A61L 27/38, A61L 27/36

(21) Application number: **04251928.0**

(22) Date of filing: **31.03.2004**

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PL PT RO SE SI SK TR
Designated Extension States:
AL LT LV MK

(30) Priority: **31.03.2003 US 405062**

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(54) Intervertebral fusion implant

(57) An intervertebral fusion device, a method of making the intervertebral fusion device, and a method of using the intervertebral fusion device to promote fusion between two consecutive vertebrae in a patient is described. The intervertebral fusion device has an intervertebral fusion cage that has a load bearing wall, and a porous matrix adjacent to the load bearing wall. The load bearing wall of the fusion cage has a greater density than the internal porous matrix. The open pores of the porous matrix define an inner surface to which one or more agents that promote bone growth are attached.

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Printed by Jouve, 75001 PARIS (FR)

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Description

[0001] Implantable intervertebral fusion devices are routinely used by surgeons to treat degenerative disc disease, discongenic lower back pain, spondylolisthesis, ruptured discs due to injury and other spinal conditions. Fusion devices are used to keep adjacent vertebrae in the correct spaced apart position while bone growth takes place to complete the fusion of the adjacent vertebrae. Typically, intervertebral fusion devices are hollow cages with side walls made from stainless steel, cobalt or titanium alloy which provide strength to support intervertebral forces. The hollow space between the side walls is usually filled with bone graft material that is either provided by the patient (autogenous) or provided by a third party donor (allogenous).

[0002] Unfortunately, the metallic supporting frame of the prior art fusion cages is not osteoconductive and therefore does not form a strong mechanical attachment to a patient's bone tissue. This can lead to graft necrosis, poor fusion and poor stability. In addition, the prior art fusion cages must be filled with autologous bone graft material or allograft bone material. However, the supply of autologous bone material is limited and significant complications can occur from the bone harvesting procedure. Moreover, the patient must undergo two separate incisions which may increase the pain and recuperation time of the patient. Allograft bone material is also in limited supply and carries a risk of disease transmission.

[0003] In view of the problems discussed above, a sugnificant need exist for further improvement in the design of spinal fusion devices.

[0004] The instant invention relates to an intervertebral fusion device, a method of making the intervertebral fusion device and a method of using the intervertebral fusion device to promote fusion between two consecutive vertebrae in a patient. The intervertebral fusion device has an intervertebral fusion cage that has a load bearing wall, and a porous matrix adjacent to the load bearing wall. In a preferred embodiment, the porous matrix is integrally bound to the load bearing wall. The load bearing wall of the fusion cage has a higher compression strength than the internal porous matrix. The open pores of the porous matrix define an inner surface to which one or more agents that promote bone growth are attached. In one embodiment, the agent that promotes bone growth is analogous and is present in a concentration of about 5 times to about 30 times greater than the concentration found in the patient's bone marrow aspirate or platelet rich plasma. Preferably, the agent is mesenchymal stem cells. In another embodiment, at least one of the agents that promotes bone growth is a concentrated growth factor.

[0005] The intervertebral fusion devices preferably are fabricated by passing a solution comprising one or more agents that promote bone growth through the porous matrix of the fusion cage, thereby attaching the agent to the inner surface.

[0006] The intervertebral fusion device can be used to promote fusion of two adjacent vertebrae in a mammal, preferably a human patient. In this method, a solution that has one or more bone growth promoting agents is passed through the intervertebral fusion cage, thereby attaching the agent to the inner surface, then the fusion cage is inserted into the intervertebral space between the two vertebrae of the mammal. In a preferred embodiment, the patient's own bone marrow aspirate or platelet rich plasma is passed through the porous matrix during the surgical procedure to insert the fusion cage. The fusion cage may be inserted into the intervertebral space of a mammal from either the anterior or posterior side of the mammal using surgical techniques known to those skilled in the art.

[0007] One advantage of the intervertebral fusion device of the invention is that the device supplies a concentrated amount of mesenchymal stem cells (MSC's) from the bone marrow aspirate, and so does not require autologous bone taken from the iline crest (which requires a second operation) or allograft bone material (which may be in limited supply). In addition, there is no risk disease transmission, as when allograft bone material is used.

[0008] The Figure is a schematic representation of a preferred embodiment of an intervertebral fusion device of the invention.

[0009] The present invention relates to a new and improved intervertebral fusion device that has a load bearing wall that can support intervertebral forces and a porous matrix having agents that promote bone growth attached the inner surface of the pores. Typically, the load bearing wall is made of a material that is denser than the porous matrix and can support a load in the range of al least about 8.2 kN (kilonewtons). This typically requires that the load bearing wall to be made of a material having a compression strength of between about 1000 MPa and 1500 MPa. In a preferred embodiment, the porous matrix is integrally bound to the load bearing wall. The fusion cage may have more than one load bearing wall. In a preferred embodiment, the fusion cage has at least two load bearing walls.

[0010] A preferred embodiment of an intervertebral fusion device (1) of the invention is seen in the Figure. The device has two load bearing walls (3) which are adjacent to a porous matrix (5) and an upper surface (7) and a lower surface (9) that will contact the vertebrae to be fused when the device is inserted into the intervertebral space. The device is configured so that the upper and lower surfaces are sufficiently loaded to produce bone growth.

[0011] The fusion cage can be made of any biocompatible material and has a suitable size and shape for seated implantation into the intervertebral space. In some embodiments, the load bearing wall of the fusion cage is approximately parallel to the spinal column when the device is inserted into the intervertebral space. In

others, the load bearing wall is angled to produce lordosis. In one embodiment, the fusion cage has a surface at each end of the load bearing wall which will contact the two vertebrae to be fused when the cage is inserted and are approximately perpendicular to the load bearing wall. In another embodiment, the two surfaces that contact the vertebrae to be fused are not perpendicular to the load bearing wall, but instead are tapered in the anterior to posterior direction to achieve lordosis or in the posterior to anterior direction to achieve kyphosis. In a preferred embodiment, the surfaces of the fusion cage that contact the vertebrae to be fused have ridges or feeth to prevent increase the stability of the fusion device once it is inserted into the patient. Optionally, the fusion cage can be a series of cages stacked on top of each other, such as described in U.S. Patent Nos. 6,195,211 and 5,192,327, the entire teachings of which are incorporated herein by reference.

[0012] Mechanical attachment of the porous matrix to the load bearing wall may be achieved by, for example, press fitting a porous matrix cylinder into a hollow sleeve, or by sintering to achieve an integral attachment. Preferably, the load bearing wall and the porous matrix of the fusion cage are made of the same material. However, the load bearing wall generally will have a density that is greater than the porous matrix. Typically, the load bearing wall will have a porosity in the range of between 0 and about 5 vol%, whereas the porous matrix will typically have a porosity in the range of between about 40 vol% and about 80 vol%. In a preferred embodiment, the pores have an average diameter in the range of between about 25 μm and about 1000 μm. More preferably, the average diameter of the pores is between about 100 μm and about 500 μm.

[0013] In one embodiment, the fusion cage of the invention may be made of a symthetic materical, preferably one that is stronger than bone, preferably, it is a sintered ceramic, such as an oxide of alumina, ziriconia, or a combination thereof. In ceramic materials, the pore size can be controlled by conventional techniques, such as controlling the temperature during the sintering process. Ceramic sintering techniques are known to those skilled in the art. In a preferred embodiment, the ceramic includes an osteoconductive material, such as hydroxyapatite or tricalcium phosphate, to promote bone growth into the fusion device. In one embodiment, the osteoconductive material may be added as a coating on the inner surface of the porous matrix.

[0014] Other suitable materials for the fusion cage include biopolymers such as, for example, polylactic acid, polyglycolic acid, a copolymer of polylactic acid and polyglycolic acid, a polyarylethyl ketone, polygalactic acid, polycaprolactone, polyethylene oxide, polypropylene oxide, polysulfone, polyethylene, polypropylene, a polyaryletherketone, and combinations thereof. In one embodiment, the fusion cage comprises a polyaryletherketone. In a preferred embodiment, the percentage of the fusion cage that is a polyaryletherketone is in the range of between about 40 vol% and about 90 vol%. In another embodiment, the polyaryletherketone is mixed with carbon fibers which are typically chopped. In a preferred embodiment, the percentage of the fusion cage that is carbon fiber is in the range of between about 1 vol% and about 60 vol%. Examples of polyaryletherketones include polyetheretherketone, poly(arylether ketone ketone), and polyetherketone.

[0015] An agent that promotes bone growth is attached to the inner surface of the porous matrix. Agents that promote bone growth include connective tissue progenitor cells (referred to as "progenitor cells" herein) and growth factors. The agent that promotes bone growth is attached to the inner surface, and thereby concentrated, by parsing a solution containing the agent through the porous matrix one or more times. Typically, the concentration of the agent that promotes bone growth is increased in the range of between about 2 fold and about 30 fold by passing the solution through the porous matrix of the fusion cage. More preferably, the agent is increased in the range of between about 5 fold to about 20 fold, and more preferably between about 5 fold and 10 fold.

[0016] The term "progenitor cells," as used herein, are cells that are capable of differentiating into cartilage or bone. Examples of progenitor cells include mesenchyntal stem cells, hematopoiete cells, and embryonic stem cells. In one embodiment, progenitor cells are attached to the inner surface of the porous matrix by passing bone marrow aspirate suspension through the fusion cage.

[0017] As used herein, the term "growth factors" encompasses any cellular product that modulates the growth or differentiation of other cells, particularly connective tissue progenitor cells. Growth factors include, but are not limited to, isoforms of platelet derived growth factors (PDGF), fibroblast growth factors, epithelial growth factors, isoforms of transforming growth factor Beta, insulin-like growth factors, bone morphogenic proteins and precursors thereof. In a preferred embodiment, the growth factor is a bone morphogenic protein or a precursor thereof. In one embodiment, growth factors are attached to the inner surface of the porous matrix by passing platelet rich plasma or bone marrow aspirate suspension through the fusion cage. In another embodiment, growth factors are attached to the inner surface of the porous matrix by passing a solution of recombinant growth factors through the fusion cage.

[0018] Bone marrow aspirate contains plasma, nucleated connective tissue progenitor cells, nucleated hematopoietic cells, endothelial cells, and cells derived from contaminating peripheral blood, including red cells and platelets. Since bone marrow aspirate also contains peripheral blood, it is preferred that the bone marrow be collected in a syringe containing an anti-coagulant. Suitable anti-coagulants include, for example, heparin, sodium citrate, and EDTA. Preferably, the bone marrow aspirate is mixed with a sterile isotonic solution to provide a concentration in the range of from about 10 million to

about 300 million nucleated cells/ml, preferably from about 20 million to about 250 million nucleated cells/ml, more preferably from about 50 million to about 200 million nucleated cells/ml. Suitable isotonic solutions include, for example, isotonic buffered salt solutions, such as Hank's Balanced Salt Solution and phosphate buffered saline, and tissue culture medium such as minimal essential medium. As used herein, the term "bone marrow aspirate suspension" refers to a bone marrow aspirate that has not been mixed with an isotonic solution and to a bone marrow aspirate that has been mixed with an isotonic solution.

[0019] Platelet rich plasma typically is produced from centrifuging blood and isolating the buffy coat produced therefrom, and may be produced from the blood of the patient receiving the intervertebral fusion device, by methods known to these skilled in the art. Platelet rich plasma contains densely concentrated platelets (which, when activated by thrombin, release growth factors).

[0020] In some embodiments, a concentrated fraction of either the BMA or PRP is passed through the porous matrix. Preferably, this concentrated fraction is the buffy coat.

[0021] To allow for implantation of the graft into a mammal, it is preferred that the fusion cage be sterile. Preferably, the bone marrow aspirate suspension is permitted to flow through the sterile fusion cage under hydrostatic pressure which may be generated by external forces or by the force of gravity. Preferably, the linear elution rate of the suspension through the fusion cage is between 2 and 500 mm/minute, more preferably between 5 and 200 mm/minute, most preferably between 10 and 100 mm/minute.

[0022] Optionally, the effluent is collected sterilely in an effluent collector and recycled through the fusion cage one or more times to increase the number of connective tissue progenitor cells attached to the inner surface of the porous matrix of the fusion cage.

[0023] In some embodiments, the device further comprises cell adhesion molecules attached to the inner surface of the porous matrix. These molecules help the device retain the agents passing therethrough.

[0024] Optionally, a wash solution is passed through the fusion cage after the original bone marrow aspirate suspension and any effluents have been passed through the fusion cage. Preferably, the wash solution comprises a sterile, isotonic, buffered solution having a pH range of 7.3 to 7.5. Suitable wash solutions include, for example, phosphate-buffered saline, Hank's balanced salt solution, and minimal essential medium.

[0025] Optionally, growth factors or additional cells which secrete or present (i.e., express on their surface) growth factors are attached to the inner surface of the porous matrix prior to use, i.e, before, during or after the time the bone marrow aspirate suspension is passed through the fusion cage. Growth factors which may be added include for example, isoforms of platelet derived growth factors, fibroblast growth factors, epithelial growth factors, transforming growth factor Beta, insulin-like growth factor(s), parathyroid hormone (PTH) or PTH related peptide, and bone morphogenic proteins and precursors thereof. Preferably, growth factors are added by passing a solution containing the growth factors through fusion cage after all previous suspensions and solutions have been passed through the substrate. Alternatively, grow factors are added by incorporation into the wash solution. Platelets, which are known to secrete growth factors and to adhere to negatively charged surfaces, are added to the graft by passing a suspension of platelets, such as blood or platelet concentrate which contains an anti-coagulant, through the fusion cage.

[0026] In devices designed for posterior lumbar interbody fusion (PLIF), the present invention is advantageous over conventional autograft-containing cages in that there is less of a chance that the graft will fall out of the cage during the high-impact insertion of the cage.

EQUIVALENTS

[0027] While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

Claims

1. An intervertebral fusion device, comprising:

   a) an intervertebral fusion cage, comprising

      i) a load bearing wall; and
      ii) a porous matrix mechanically attached to the load bearing wall, wherein the open pores of the porous matrix define an inner surface; and

   b) one or more agents that promote bone growth attached to the inner surface wherein the agent is selected from the group consisting of: an agent being about 5 times to about 30 times more concentrated than the concentration found in bone marrow aspirate or platelet rich plasma; and/or the agent is a concentrated growth factor.

2. The device of claim 1, wherein one or more of the agents that promote bone growth are progenitor cells; and optionally wherein the progenitor cells are:

   a) concentrated by passing a solution of platelet rich plasma or bone marrow aspirate suspension through the porous matrix one or more

times; and/or
b) are selected from the group consisting of mesenchymal stem cells, hematopoietic cells, embryonic stem cells and combinations thereof.

3. The device of claim 1 or claim 2, further comprising a growth factor, and optionally wherein the growth factor:

a) is concentrated by passing a solution comprising a recombinant growth factor through the porous matrix one or more times;
b) is concentrated by passing a solution of platelet rich plasma or bone marrow aspirate suspension through the porous matrix one or more times; and/or
c) is selected from the group consisting of bone morphogenic protein or a precursor thereof, isoforms of platelet derived growth factors, fibroblast growth factors, epithelial growth factors, isoforms of transforming growth factor Beta, insulin-like growth factors, and combinations thereof, preferably wherein the growth factor is bone morphogenic protein or a precursor thereof.

4. The device of claim 1, claim 2 or claim 3, wherein the fusion cage comprises:

a) a ceramic, and optionally wherein the ceramic is an oxide of alumina, zirconia or a combination thereof, and further optionally wherein the ceramic comprises hydroxyapatite, tricalcium phosphate, or a combination thereof;
b) a biopolymer; and optionally wherein the biopolymer is selected from the group consisting of a polylactic acid, polyglycolic acid, a copolymer of polylactic acid and polyglycolic acid, a polyarylethyl ketone, polygalactic acid, polycaprolactone, polyethylene oxide, polypropylene oxide, polysulfone, polyethylene, polypropylene, a polyaryletherketone and combinations thereof;
c) a polyaryletherketone selected from the group consisting of polyetheretherketone, poly (arylether ketone ketone), polyetherketone, and combinations thereof; and optionally wherein the fusion cage further comprises carbon fibers; and further optionally wherein the composition of the fusion cage is between about 40% and about 60% polyaryletherketone; and/or the composition of the fusion cage is between about 1 % and about 60% carbon fiber.

5. The device according to any one of the preceding claims, wherein:

a) the porous matrix is integrally bound to the load bearing wall;
b) the porous matrix has a porous volume of between about 40% and about 80%; and/or
c) the porous matrix has an average pore diameter of between about 25µm and about 1000µm; and/or
d) the load bearing wall has an upper and lower bearing surfaces that have teeth; and/or
e) the fusion cage is tapered in the anterior to posterior direction to achieve lordosis; and/or
f) the fusion cage is tapered in the posterior to anterior direction to achieve kyphosis; and/or
g) the device comprises more than one fusion cage stacked on top of each other.

6. A method of fabricating an intervertebral fusion device, comprising the steps of:

a) providing an intervertebral fusion cage, comprising:

i) a load bearing wall; and
ii) a porous matrix mechanically attached to the load bearing wall, wherein the open pores of the porous matrix define an inner surface; and

b) passing a solution comprising one or more agents that promote bone growth through the porous matrix, thereby attaching the agent to the inner surface.

7. The method of claim 6, wherein the solution comprises progenitor cells, and optionally wherein the progenitor cells are selected from the group consisting of mesenchymal stem cells, hematopoiete cells, embryonic stem cells, and combinations thereof; and/or the solution is platelet rich plasma or bone marrow aspirate suspension.

8. The method of claim 6 or claim 7, wherein the solution comprises a growth factor, and optionally wherein:

a) the growth factor is selected from the group consisting of bone morphogenic protein or a precursor thereof, isoforms of platelet derived growth factors, fibroblast growth factors, epithelial growth factors, isoforms of transforming growth factor Beta, insulin-like growth factors, and combinations thereof;
b) the growth factor is bone morphogenic protein or a precursor thereof; and/or
c) the solution comprises a recombinant growth factor; and/or
d) the solution is platelet rich plasma or bone marrow aspirate suspension.

9. An intervertebral fusion device fabricated using the method of any one of claims 6 to 8.

10. A method of promoting fusion of two consecutive vertebrae in a mammal, comprising the steps of:

a) providing an intervertebral fusion cage, comprising:

i) a load bearing wall; and
ii) a porous matrix mechanically attached to the load bearing wall, wherein the open pores of the porous matrix define an inner surface; and

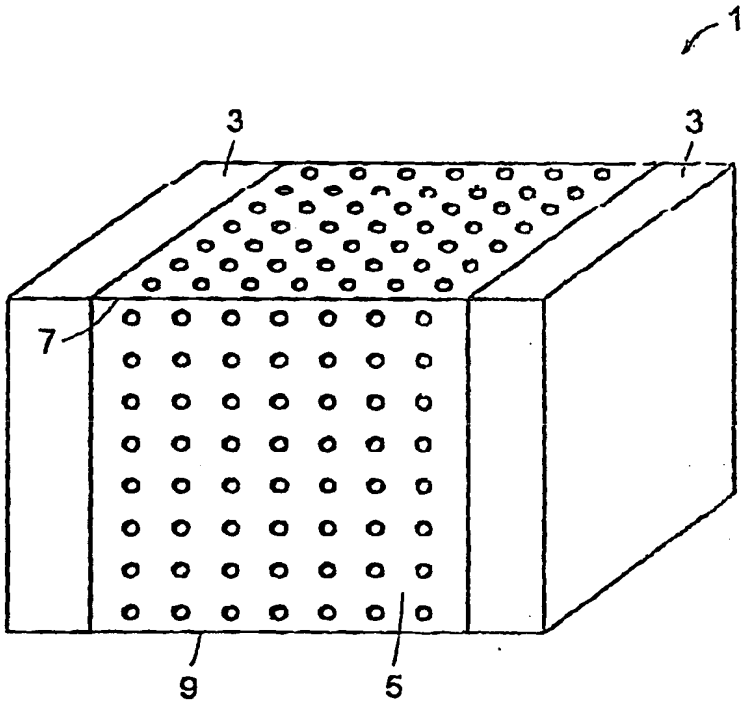
b) passing a solution comprising one or more agents that promote bone growth through the porous matrix, thereby attaching the agent to the inner surface; and
c) inserting the fusion cage containing the agent into the intervertebral space between the two vertebrae.

11. The method of claim 10, wherein the solution comprises progenitor cells; and optionally wherein:

a) the progenitor cells are selected from the group consisting of mesenchymal stem cells, hematopoiete cells, embryonic stem cells, and combinations thereof; and/or
b) the solution is platelet rich plasma or bone marrow aspirate suspension, and in which case optionally wherein the solution is an autologous solution; and/or the solution is passed through the porous matrix during a surgical procedure to insert the fusion cage; and/or
c) the solution comprises a growth factor, and optionally:

(i) wherein the growth factor is selected from the group consisting of bone morphogenic protein or a precursor thereof, isoforms of platelet derived growth factors, fibroblast growth factors, epithelial growth factors, Isoforms of transforming growth factor Beta, insulin-like growth factors, and combinations thereof, preferably the growth factor is bone morphogenic protein or a precursor thereof; and/or
(ii) the solution comprises a recombinant growth factor;

d) the fusion cage is inserted from the anterior side of the mammal; and/or
e) the fusion cage is inserted from the posterior side of the mammal.



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PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 04 25 1928

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	WO 01/70139 A (SYNTHES AG ;ANGELUCCI CHRISTOPHER M (US); SYNTHES USA (US); PAUL D) 27 September 2001 (2001-09-27)	1-9	A61F2/44 A61L27/38 A61L27/36
Y	* page 6, line 3 - line 20 * * page 9, line 5 - page 10, line 3 * * page 11, line 7 - line 11 * * page 14, line 16 - line 18 * * page 18, line 7 - line 14 *	1-8	
X	DE 44 09 836 A (DRAENERT KLAUS) 28 September 1995 (1995-09-28) * column 4, line 1 - column 5, line 12 *	1-4,6-8	
Y	US 2003/031695 A1 (KADIYALA SUDHAKAR ET AL) 13 February 2003 (2003-02-13) * paragraph [0008] - paragraph [0021] * * paragraph [0126] *	1-5,7,8	
Y	US 6 037 519 A (MCKAY WILLIAM F) 14 March 2000 (2000-03-14) * column 4, line 1 - line 45 * * column 6, line 46 - column 8, line 11 *	1,3-6,8	
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TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61F
A61L
A61K

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

1-9

Claims searched incompletely :

Claims not searched :

10,11

Reason for the limitation of the search:

Article 52 (4) EPC - Method for treatment of the human or animal body by surgery

Place of search	Date of completion of the search	Examiner
MUNICH	9 July 2004	Buchmann, G

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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T : theory or principle underlying the invention
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EPO FORM 1503 03.82 (P04C07)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 04 25 1928

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	US 5 197 985 A (HAYNESWORTH STEPHEN E ET AL) 30 March 1993 (1993-03-30) * column 1, line 58 - column 2, line 38 * -----	1-9	TECHNICAL FIELDS SEARCHED (Int.Cl.7)

EPO FORM 1502 03.82 (P04C10)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 04 25 1928

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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09-07-2004

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0170139 A	27-09-2001	WO 0170139 A2	27-09-2001
		AU 4936701 A	03-10-2001
		CA 2403688 A1	27-09-2001
		EP 1265557 A2	18-12-2002
		AU 4936801 A	03-10-2001
		AU 4936901 A	03-10-2001
		CA 2403672 A1	27-09-2001
		CA 2403683 A1	27-09-2001
		EP 1265555 A2	18-12-2002
		EP 1296620 A2	02-04-2003
		WO 0170136 A2	27-09-2001
		WO 0170137 A2	27-09-2001
		US 2004075192 A1	22-04-2004
		US 2001039456 A1	08-11-2001
		US 2002029084 A1	07-03-2002
		US 2001056302 A1	27-12-2001
		US 2001039458 A1	08-11-2001
		US 2001039457 A1	08-11-2001
		US 2001041941 A1	15-11-2001
DE 4409836 A	28-09-1995	DE 4409836 A1	28-09-1995
		WO 9525483 A1	28-09-1995
US 2003031695 A1	13-02-2003	US 6541024 B1	01-04-2003
		AU 731468 B2	29-03-2001
		AU 2462297 A	12-11-1997
		CA 2251983 A1	30-10-1997
		EP 0906415 A1	07-04-1999
		JP 2000508911 T	18-07-2000
		WO 9740137 A1	30-10-1997
US 6037519 A	14-03-2000	US 6346123 B1	12-02-2002
US 5197985 A	30-03-1993	US 6010696 A	04-01-2000
		US 5733542 A	31-03-1998
		US 5811094 A	22-09-1998
		US 5837539 A	17-11-1998

EPO FORM P0459

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